Complete Summary

GUIDELINE TITLE

Guide to anticoagulant therapy: heparin: a statement for healthcare professionals from the American Heart Association.

BIBLIOGRAPHIC SOURCE(S)

Hirsh J, Anand SS, Halperin JL, Fuster V. AHA Scientific Statement: Guide to anticoagulant therapy: heparin: a statement for healthcare professionals from the American Heart Association. Arterioscler Thromb Vasc Biol 2001 Jul;21(7):E9-9. [285 references] PubMed

Hirsh J, Anand SS, Halperin JL, Fuster V. Guide to anticoagulant therapy: heparin. A statement for healthcare professionals from the American Heart Association. Circulation 2001 Jun 19;103(24):2994-3018. [285 references] PubMed

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]); coronary artery disease; unstable angina and non-Q-wave myocardial infarction (MI);acute myocardial infarction; coronary thrombolysis; thrombotic occlusion during percutaneous transluminal coronary angioplasty; ischemic stroke and systemic embolism in atrial fibrillation (AF); and thromboembolism during trauma and general and orthopedic surgery

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Hematology
Internal Medicine
Neurological Surgery
Orthopedic Surgery
Surgery

INTENDED USERS

Health Care Providers
Physicians

GUIDELINE OBJECTIVE(S)

To provide recommendations for the clinical use of heparins and low-molecular-weight heparins (LMWHs)

TARGET POPULATION

Patients requiring anticoagulant therapy

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation/Monitoring

1. Activated partial thromboplastin time (aPTT)
2. 2-dimensional echocardiography
3. Determination of International Normalized Ratio (INR)
4. Activated clotting time (ACT)

Management/Treatment

1. Heparin
2. Unfractionated heparins (UH)
3. Low-molecular-weight heparins (LMWHs) including:
   - Reviparin sodium
   - Tinzaparin
   - Nadroparin
   - Enoxaparin
   - Dalteparin
4. Thrombolytic therapy including streptokinase
5. Platelet glycoprotein (GP) IIb/IIIa antagonists including:
   - Dipyridamole
   - Lamifiban
   - Tirofiban
   - Abciximab
   - Eptifibatide (Integrilin)
6. Aspirin
7. Warfarin

8. Anisoylated plasminogen-streptokinase activator complex (APSAC)
9. Tissue plasminogen activator
10. Nitroglycerin
11. Ticlopidine
12. Thrombin inhibitors including:
   - Lepirudin (Refludan)
   - Hirudin

MAJOR OUTCOMES CONSIDERED

- Predictive value of diagnostic tests
- Incidence of recurrent venous thromboembolism
- Incidence of minor and major hemorrhage
- Morbidity and mortality
- Length of hospital stay
- Incidence of fatal or nonfatal myocardial infarction (MI)
- Recurrent angina
- Coronary artery patency

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee in December 2000. It was published in Circulation 2001;103:2994-3018.

<div style="background-color:teal; color:white; text-align:center;">RECOMMENDATIONS</div>

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): The second version of "A Guide to Anticoagulant Therapy" was published in 1994. Since then, the following important advances have been made: (1) low-molecular-weight heparin (LMWH) preparations have become established anticoagulants for treatment of venous thrombosis and have shown promise for the treatment of patients with acute coronary syndromes; (2) direct thrombin inhibitors have been evaluated in venous thrombosis and acute coronary syndromes; (3) important new information has been published on the optimal dose/intensity for therapeutic anticoagulation with coumarin anticoagulants; and (4) the dosing of heparin for adjunctive therapy in patients with acute coronary syndromes has been reduced because conventional doses cause serious bleeding when combined with thrombolytic therapy or glycoprotein (GP) IIb/IIIa antagonists. The recommendations in this review provide updated information on these advances.

Dose-Response Relationships and Laboratory Monitoring

The risk of heparin-associated bleeding increases with dose and with concomitant thrombolytic or abciximab therapy. The risk of bleeding is also increased by recent surgery, trauma, invasive procedures, or concomitant hemostatic defects. Randomized trials show a relationship between the dose of heparin administered and both its efficacy and its safety. Because the anticoagulant response to heparin varies among patients with thromboembolic disorders, it is standard practice to adjust the dose of heparin and monitor its effect, usually by measurement of the

activated partial thromboplastin time (aPTT). This test is sensitive to the inhibitory effects of heparin on thrombin, factor Xa, and factor IXa. Because there is a relationship between heparin dose and both anticoagulant effect and antithrombotic efficacy, it follows that there should be a relationship between anticoagulant effect and antithrombotics efficacy.

In the past, researchers were secure in the contention that a strong relationship existed between the ex vivo effect of heparin on the aPTT and its clinical effectiveness, but several lines of evidence have challenged the strength of such a relationship. First, the initial findings supporting a tight relationship between the effect of heparin on aPTT and its clinical efficacy were based on retrospective subgroup analysis of cohort studies and are therefore subject to potential bias (See table 3 of the original guideline). Second, the results of a randomized trial and 2 recent meta-analyses of contemporary cohort studies call into question the value of the aPTT as a useful predictor of heparin efficacy in patients with venous thrombosis. Third, no direct relationship between aPTT and efficacy was observed in the subgroup analysis of the GUSTO-I study (Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries) in patients with acute myocardial infarction (MI) who were treated with thrombolytic therapy followed by heparin. Fourth, even if the aPTT results were predictive of clinical efficacy, the value of this test would be limited by the fact that commercial aPTT reagents vary considerably in responsiveness to heparin. Although standardization can be achieved by calibration against plasma heparin concentration (the therapeutic range is 0.2 to 0.4 U/mL based on protamine titration or 0.3 to 0.7 U/mL based on anti-factor Xa chromogenic assay), this is beyond the scope of many clinical laboratories. Heparin monitoring is likely to become less problematic in the future as low-molecular-weight heparin (LMWH) replaces unfractionated heparin (UFH) for most indications.

Despite its limitations for monitoring heparin, aPTT remains the most convenient and most frequently used method for monitoring the anticoagulant response. aPTT should be measured approximately 6 hours after the bolus dose of heparin, and the continuous intravenous (IV) dose should be adjusted according to the result. Various heparin dose-adjustment nomograms have been developed (See table 4 and 5 of the original guideline document), but none are applicable to all aPTT reagents, and the therapeutic range must be adapted to the responsiveness of the reagent used. In addition, the dosage regimen should be modified when heparin is combined with thrombolytic therapy or platelet glycoprotein (GP) IIb/IIIa antagonists. When heparin is given by subcutaneous (SC) injection in a dose of 35,000 U/24 hours in 2 divided doses, the anticoagulant effect is delayed approximately 1 hour, and peak plasma levels occur after approximately 3 hours.

Limitations of Heparin

The limitations of heparin are based on its pharmacokinetic, biophysical, and nonanticoagulant biological properties. All are caused by the antithrombin (AT)-independent, charge-dependent binding properties of heparin to proteins and surfaces. Pharmacokinetic limitations are caused by AT-independent binding of heparin to plasma proteins, proteins released from platelets, and possibly endothelial cells, resulting in the variable anticoagulant response to heparin and the phenomenon of heparin resistance. AT-independent binding to macrophages and endothelial cells also results in a dose-dependent mechanism of heparin

clearance. Refer to the original guideline for further discussion of these limitations.

Clinical Use of Heparin

Heparin is effective for the prevention and treatment of venous thrombosis and pulmonary embolism (PE), for prevention of mural thrombosis after MI, and for treatment of patients with unstable angina and MI. Although heparin is used to prevent acute thrombosis after coronary thrombolysis, recent reports question the benefits of heparin in this setting when patients are also treated with aspirin (see below).

In patients with venous thromboembolism or unstable angina, the dose of heparin is usually adjusted to maintain aPTT at an intensity equivalent to a heparin level of 0.2 to 0.4 U/mL as measured by protamine titration or an anti-factor Xa level of 0.30 to 0.7 U/mL. For many aPTT reagents, this is equivalent to a ratio (patient/control aPTT) of 1.5 to 2.5. The recommended therapeutic range is based on evidence from animal studies and supported by subgroup analysis of prospective cohort studies involving treatment of deep vein thrombosis (DVT), prevention of mural thrombosis after MI, and prevention of recurrent ischemia after coronary thrombolysis. Recommended heparin regimens for venous and arterial thrombosis are summarized in the table below.

Table: Clinical Use of Heparin

Condition	Recommended Heparin Regimen
Venous thromboembolism	
Prophylaxis of DVT and PE	5,000 U SC every 8 or 12 hours or adjusted low-dose heparin*
Treatment of DVT	5,000 U IV bolus followed by 32,000 U per 24 hours by IV infusion or 35,000 to 40,000 U per 24 hours SC, adjusted to maintain aPTT* in the therapeutic range
Coronary heart disease	
Unstable angina or acute MI without thrombolytic therapy	5,000 U IV bolus followed by 32,000 U per 24 hour IV infusion adjusted to maintain aPTT in the therapeutic range
Acute MI after thrombolytic therapy**	5,000 U IV bolus followed by 24,000 U per 24 hours adjusted to maintain aPTT in the therapeutic range

*Note: aPTT varies in responsiveness to heparin.
**Note: The role of heparin is unproven.

Treatment of Venous Thromboembolism

Use of heparin for the treatment of venous thrombosis and PE is based on results of randomized studies. The effectiveness and safety of heparin administered by continuous IV infusion have been compared with intermittent IV injection in 6

studies and with high-dose SC heparin in 6 studies. It is difficult to determine the optimal route of heparin administration because different doses were used in these studies, most of the studies were small and underpowered, and different criteria were used to assess efficacy and safety. Nevertheless, the results indicate that heparin is safe and effective when appropriate doses are given. Thus, in a recent pooled analysis of 11 clinical trials in which approximately 15,000 patients were treated with either heparin (administered as an initial bolus of 5,000 U followed by 30,000 to 35,000 U/24 hours with aPTT monitoring) or SC LMWH, the mean incidence of recurrent venous thromboembolism among patients assigned heparin was 5.4%. The rate of major bleeding was 1.9%, fatal recurrent venous thromboembolism occurred in 0.7%, and bleeding was fatal in 0.2% of heparin-treated patients. The initial dose of heparin is particularly critical when heparin is administered by SC injection, because an adequate anticoagulant response is not achieved in the first 24 hours unless a high starting dose is used (17,500 U SC).

Audits of heparin monitoring practices indicate that dosage adjustments are frequently inadequate, and dosing practices can be improved by use of a simple and effective weight-adjusted dosage regimen. There is evidence that a 5-day course of heparin is as effective as a 10-day course (See table 7 of the original guideline document). The short-course regimen has obvious appeal, reducing hospital stay and the risk of heparin-induced thrombocytopenia (HIT). Although the shorter course of treatment can be recommended for most patients with venous thromboembolism, this may not be appropriate in cases of extensive iliofemoral vein thrombosis or major PE, because such patients were underrepresented in these studies.

Prophylaxis of Venous Thromboembolism

Heparin in a fixed low dose of 5,000 U SC every 8 or 12 hours is an effective and safe form of prophylaxis in medical and surgical patients at risk of venous thromboembolism. Low-dose heparin reduces the risk of venous thrombosis and fatal PE by 60 to 70%. Among general surgical patients, the incidence of fatal PE was reduced from 0.7% in controls to 0.2% in one study (P<0.001) and from 0.8% to 0.3% (P<0.001) in a larger analysis that included orthopedic surgical patients. There was also a small but statistically significant decrease in mortality from 3.3% to 2.4% with low-dose heparin prophylaxis (P<0.02). The use of low-dose heparin is associated with a small excess incidence of wound hematoma and a minimal, statistically insignificant increase in major bleeding but no increase in fatal bleeding. Low-dose heparin also effectively prevents venous thromboembolism in patients with MI and in those with other serious medical disorders, and it reduced in-hospital mortality by 31% (P<0.05) in a study of 1,358 general medical patients aged >40 years. Although low-dose heparin is also effective in reducing DVT after hip surgery, the incidence of thrombosis remains substantial (20 to 30%) and can be reduced further with either adjusted low-dose heparin or fixed-dose LMWH. Moderate-dose warfarin is effective in patients undergoing major orthopedic surgical procedures, but direct comparisons of low-dose heparin and warfarin have not been performed in major orthopedic surgery.

Coronary Artery Disease

Coronary thrombosis is important in the pathogenesis of unstable angina, acute MI, and sudden cardiac death. It is also important in the pathogenesis of

reinfarction and death in patients with acute MI treated with thrombolytic agents or percutaneous transluminal coronary angioplasty. In most patients, heparin ameliorates the thrombotic manifestations of acute coronary syndromes, but it is no longer used as the sole antithrombotic drug in these settings. Today, heparin is always used in combination with aspirin in potentially eligible patient groups with acute myocardial ischemia, in those receiving thrombolytic therapy for evolving MI, in those treated with platelet GP IIb/IIIa antagonists for unstable angina, and in those undergoing high-risk coronary angioplasty. When combined with aspirin, thrombolytic agents, or GP IIb/IIIa antagonists, however, heparin in full doses increases the risk of bleeding, and the dose is usually reduced in these settings.

Unstable Angina and Non-Q-Wave MI

Heparin has been evaluated in a number of randomized, double-blind, placebo-controlled clinical trials for the short-term treatment of unstable angina or non–Q-wave MI. When given alone to patients with unstable angina, heparin is effective in preventing acute MI and recurrent angina, and when used in combination with aspirin, the results of a meta-analysis of 6 small trials suggest that the combination also reduces short-term rates of cardiovascular death and MI by approximately 30% over those achieved with aspirin alone.

One study compared the relative efficacy and safety of heparin, aspirin, and their combination in 479 patients with unstable angina. Heparin was administered as an initial 5,000-U IV bolus, followed by IV infusion of 1,000 U/h, adjusted to maintain the aPTT at 1.5 to 2.0 times the control value. Treatment was initiated within 24 hours after the onset of chest pain and continued for approximately 6 days. The incidence of MI during the acute period was 11.9% in the placebo group and was reduced to 3.3% in the aspirin groups (P=0.012), 0.8% in the heparin group (P<0.0001), and 1.6% in the group given the combination of aspirin and heparin (P=0.001). The incidence of refractory angina (22.9% in the placebo group) was significantly reduced to 8.5% (P=0.002) in the heparin group and 10.7% in the heparin-plus-aspirin group (P=0.11) but was 16.5% in the aspirin group. In a second study, the same investigators compared the efficacy and safety of heparin and aspirin. This was a continuation of the previous study in which the placebo and combination groups were discontinued and an additional 245 patients were randomized to receive either continuous IV heparin or oral aspirin twice daily during the in-hospital phase (approximately 6 days). Fatal or nonfatal MI occurred during the acute period in 4 of 362 heparin-treated patients compared with 23 of 362 patients who did not receive heparin (odds ratio [OR] 0.16, P<0.005).

In contrast, the RISC (Research group in InStability in Coronary artery disease) investigators did not show that heparin was more effective than aspirin. They compared low-dose aspirin (75 mg/d) with intermittent IV heparin (10,000 U bolus every 6 hours during the initial 24 hours followed by 7,500 U every 6 hours for 5 days) in 796 men with unstable angina or non–Q-wave MI. Patients were randomized on the basis of a factorial design to treatment with heparin, aspirin, heparin plus aspirin, or placebo. The main outcome was a composite of MI or death evaluated 5 days after enrollment. The rate of this end point was 6.0% in the placebo group, 5.6% in the heparin group, 3.7% in the aspirin group, and 1.4% in the combined treatment group and was significantly reduced only with the combination (P=0.027). At 30 and 90 days, both the aspirin and aspirin-plus-

heparin groups showed significantly better results than the placebo group, but the outcome with heparin alone was no better than with placebo.

A randomized, open-label study of 214 patients with unstable angina or non–Q-wave MI assigned to either aspirin (162.5 mg/d) or aspirin plus heparin for 3 to 4 days and warfarin for up to 12 weeks after enrollment was performed. The main outcome measure was a composite of recurrent angina, MI, or death. After 12 weeks, the incidence of the main outcome was 28% for the aspirin group and 19% for the aspirin-plus-anticoagulation group (P=0.09). A meta-analysis of published data from 6 small randomized trials (n=1353 subjects), including the 3 described above, reported a risk reduction of 33% (95% confidence interval [CI] 22% to 56%) in cardiovascular death and MI with the combination of UFH and aspirin, which was of borderline significance (See figure 7 of the original guideline document).

Acute MI

Information on the benefit of heparin in patients with acute MI not given thrombolytic therapy is limited to those who were not treated with aspirin either, so the results may not be applicable to current clinical practice. An overview of randomized clinical trials performed before the reperfusion era reported a 17% reduction in mortality and a 22% reduction in reinfarction in patients assigned heparin. The control groups in these trials were not treated with aspirin, which is now considered routine.

The effect of heparin on the incidence of mural thrombosis has been evaluated in 2 randomized trials. One compared heparin in a fixed dose of 12,500 U SC every 12 hours with an untreated control group, and the other used low-dose heparin (5,000 U SC every 12 hours) for comparison. In both studies, moderate-dose heparin (12,500 U SC every 12 hours) reduced the incidence of mural thrombosis detected by 2-dimensional echocardiography by 72% and 58%, respectively (P<0.05 for each study).

Coronary Thrombolysis

Although in the past it was generally accepted that heparin was effective after coronary thrombolysis, the results of recent studies cast doubt on this view. In 3 studies that used angiographic patency as a usually surrogate end point, the combination of heparin and aspirin was not compared with aspirin alone. One study reported that a single IV bolus of 10,000 U of heparin did not improve coronary artery patency at 90 minutes. In another trial, in which heparin alone was compared with no treatment, patency of the infarct-related artery at 2 days was 71% in the heparin group and 44% in the control group (P<0.023). In the Heparin-Aspirin Reperfusion Trial, coronary artery patency at 18 hours was 82% in patients treated with heparin and 52% in a group given aspirin 80 mg/d (P<0.0002). The conclusion that heparin is more effective than aspirin in maintaining patency has been criticized because the aspirin dose was too low to completely suppress platelet thromboxane A_2 production. The results were less impressive when the combination of heparin and aspirin was compared with aspirin in a dose of 325 mg/d. In the sixth European Cooperative Study Group (ECSG-6) trial, 687 patients receiving aspirin were randomized to heparin or no heparin. Patency at a mean of 81 hours was 80% in the heparin group and 75%

in the comparison group (P<0.01). In the Australian National Heart Study Trial, 202 patients received heparin for 24 hours before randomization to either continuous IV heparin or a combination of aspirin (300 mg/d) and dipyridamole (300 mg/d). Patency after 1 week was 80% in both groups. In another study, 128 patients were treated with streptokinase and aspirin and were randomized to either an IV bolus of heparin or no heparin; the study reported no difference in coronary patency at 24 hours (86% versus 87%). The DUCCS-1 (Duke University Clinical Cardiology Studies) investigators treated 250 patients with anisoylated plasminogen-streptokinase activator complex (APSAC) and aspirin and randomized patients to heparin or no heparin. There was a small difference in coronary artery patency (80% in the heparin group versus 74% in the control group).

Two large trials, the International Study Group and the ISIS-3 (International Study of Infarct Survival) studies, assessed the value of adjunctive heparin in patients receiving thrombolytic therapy and aspirin. In both, heparin was given (12,500 U SC every 12 hours). In the International Study Group trial, heparin was begun 12 hours after randomization to fibrinolytic therapy; in the ISIS-3 trial, heparin began 4 hours after randomization.

The International Study Group study of 20,891 patients reported no difference in mortality between the heparin (8.5%) and no-heparin (8.9%) groups, whereas the risk of major bleeding was significantly increased by 0.5% in the heparin-treated group. The ISIS-3 study of 41,299 patients reported a vascular mortality rate of 10.3% in the heparin group and 10.0% in the no-heparin control group at 35 days. During the 7-day treatment period, mortality was 7.4% in the heparin group and 7.9% in the control group (P=0.06). In-hospital rates of reinfarction with heparin were 3.2% compared with 3.5% in the no-heparin group (P=0.09); stroke rates were not different. Major bleeding requiring transfusion was slightly more frequent in the heparin group (1.0% versus 0.8%, P<0.01).

In both studies, moderate doses of heparin produced marginal benefits at the cost of increased bleeding. The issue of whether IV heparin would prove more effective and at least as safe as the SC regimen used in the ISIS-3 study was addressed in the GUSTO trial, in which patients receiving streptokinase were given either a high-dose heparin regimen (5,000 U initial IV bolus, followed by an infusion of 1,000 to 1,200 U/h to maintain aPTT at 60 to 85 seconds) or the delayed SC heparin regimen used in the ISIS-3 trial. IV heparin was not superior to SC heparin among patients receiving streptokinase either in terms of mortality, reinfarction, major hemorrhage, cerebral hemorrhage, infarct-related artery patency, or arterial reocclusion.

In a much smaller study, 250 patients who had received APSAC were randomized to either aspirin alone or aspirin plus weight-adjusted IV heparin beginning 4 hours after APSAC infusion. There were no differences in ischemic outcomes, but bleeding was significantly greater with heparin (32% versus 17.2%; P =0.006). A meta-analysis composed largely of the International Study Group and ISIS-3 studies reported that, in the presence of aspirin, heparin produced a relative risk reduction of mortality of only 6% (95% CI 0% to 10%; P=0.03), representing just 5 fewer deaths per 1,000 patients treated (See table 8 of the original guideline document). There were 3 fewer reinfarctions per 1,000 (P=0.04) and 1 fewer PE per 1,000 patients (P=0.01). This small beneficial effect was associated with an

insignificant excess incidence of stroke but a definite excess of 3 major bleeding incidents per 1,000 patients (P<0.0001). In trials using high-dose heparin, there was an approximately 2-fold increase in the absolute risk of major extracranial bleeding (31 per 1,322 [2.3%] versus 14 per 1,321 [1.1%]; P=0.01).

Data on the role of adjunctive heparin in patients treated with tissue plasminogen activator are limited. From contemporary studies, Kruse and associates concluded that the role of heparin as adjunctive treatment to accelerated tissue plasminogen activator is still an open issue. A pooled analysis of 6 randomized trials exposed a trend toward reduced in-hospital mortality with heparin (9% reduction; OR 0.91, 95% CI 0.59 to 1.39) but a significantly higher rate of hemorrhagic complications when adjunctive heparin was used in tissue plasminogen activator–treated patients.

Recommendations for use of heparin in patients with acute MI are provided in the American College of Cardiology/American Heart Association guidelines. The intensity of the suggested heparin regimen is influenced by whether thrombolytic therapy is given, the type of thrombolytic agent used, and the presence or absence of risk factors for systemic embolism.

Coronary Angioplasty

Percutaneous transluminal coronary angioplasty can be complicated by early thrombotic occlusion in the instrumented artery. It is standard practice to give heparin, commencing with either an IV bolus of 10,000 U with repeated smaller bolus injections as required or as a weight-adjusted-dose regimen of 100 to 175 U/kg followed by 10 to 15 U/kg per hour. The dose is adjusted to maintain the activated clotting time (ACT) greater than 300 to 350 seconds, because there is some evidence that the complication rate is higher with lower ACT values. When these high-dose regimens are used in combination with abciximab and aspirin, however, heparin increases the risk of major bleeding. The risk can be reduced without compromising efficacy by lowering the bolus dose of heparin to 70 U/kg and giving bolus doses as needed to achieve an ACT of >200 seconds and by removing arterial sheaths when the ACT falls below 150 to 180 seconds. After coronary angioplasty, postprocedural heparin infusions are not needed for most patients who are treated with a combination of aspirin and ticlopidine.

A beneficial role for heparin has not been established when unstable angina develops within the first 6 months after coronary angioplasty. In a recent randomized trial, 200 patients who had undergone angioplasty without intracoronary stenting were randomized to IV nitroglycerin, heparin, the combination of both agents, or placebo for 63 ± 30 hours. Recurrent angina developed in 75% of patients in the placebo and heparin-alone groups compared with 42.6% of patients in the nitroglycerin-alone group and 42% of patients in the nitroglycerin-plus-heparin group (P <0.003). Refractory angina occurred in 23%, 29%, 4%, and 4% of patients, respectively (P<0.002). The OR for being event free was 0.98 (95% CI -0.55 to 1.73, P=NS) for heparin versus no heparin in this study.

Atrial Fibrillation (AF)

The role of heparin for prevention of ischemic stroke and systemic embolism in high-risk patients with nonvalvular AF has been less thoroughly investigated than oral anticoagulation with warfarin. It is likely that heparin represents an effective alternative to warfarin for antithrombotic prophylaxis, because both anticoagulants decrease hemostatic activation associated with atrial stasis in patients with this cardiac rhythm disturbance. Heparin is sometimes given as an alternative to oral anticoagulation perioperatively in patients with chronic AF who are undergoing elective surgery, but no consensus has emerged regarding when and how to substitute heparin in this situation.

Patients with AF who have sustained recent cerebral ischemic events are among those at highest risk of thromboembolism (approximately 12% per year). Oral anticoagulation reduces the risk by two thirds, similar to the benefit achieved in primary prevention. When oral anticoagulation is contraindicated, aspirin is a much less effective alternative. How rapidly and intensively to initiate anticoagulation after a cerebral ischemic event is controversial, however, considering that hemorrhagic transformation might worsen the neurological deficit.

In a study of 231 patients with nonvalvular AF and acute stroke, heparin was administered IV or SC in doses adjusted to an aPTT 1.5 to 2.0 times control values. Delay before the initiation of heparin therapy was less than 6 hours from the onset of symptoms in 74 patients and 6 to 48 hours in 157 patients. In-hospital mortality was 9%, hemorrhagic worsening occurred in 3% of patients, and stroke recurred early in 2% of patients. Neurological recovery was associated with age younger than 70 years (OR 0.2), normal baseline computed tomography (CT)-scan findings (OR 8.9), and early heparin treatment (OR 1.7, 95% CI 1.1 to 2.5), even though targeted aPTT ratios were achieved at 24 hours in fewer than 50% of patients. Stroke recurrence was associated with lower mean aPTT ratios, but higher ratios were observed in patients with symptomatic bleeding, especially on the day bleeding occurred. Neither age, initial stroke severity, blood pressure, nor baseline CT findings predicted hemorrhagic worsening. Functional recovery was improved sooner when heparin was administered early, but close monitoring of aPTT was necessary to lessen the risk of hemorrhagic complications.

Hemorrhagic transformation after acute ischemic stroke is compounded by thrombolytic therapy, but the impact of heparin can only be inferred. The Multicenter Acute Stroke Trial-Europe (MAST-E) study evaluated the safety and efficacy of streptokinase administered IV within 6 hours of stroke onset. Among 310 patients, 159 (51%) had evidence of hemorrhagic transformation on CT scan, but only 23% of these were symptomatic. The relative risk of hemorrhagic transformation after streptokinase in this trial was in the same range as in other trials of thrombolytic therapy for acute stroke. Multivariate secondary analysis found that patients with symptomatic hemorrhagic transformation were more likely to have AF and less likely to have received heparin treatment.

To minimize the risk of thromboembolism after electrical cardioversion of AF or flutter, therapeutic anticoagulation should be established for at least 3 weeks before and for 4 weeks after cardioversion when the dysrhythmia has persisted longer than 2 days or when the duration is unknown. Warfarin is usually used during the outpatient phase. A more recent approach uses transesophageal echocardiography to demonstrate the absence of thrombi in the left atrium and

left atrial appendage. If no thrombus is evident, heparin anticoagulation may be initiated before pharmacological or electrical cardioversion, followed by warfarin therapy for 1 month after cardioversion. This treatment algorithm has a safety profile similar to that of conventional therapy and minimizes both the period of anticoagulation and the duration of AF before cardioversion, but no outcome superiority has been established.

A similar rationale underlies the use of heparin in conjunction with radiofrequency catheter ablation of cardiac tachyarrhythmias. A review of the literature over the last 10 years found an overall incidence of reported thromboembolic complications of 0.6% associated with radiofrequency catheter ablation. The risk is increased (to 1.8 to 2%) when ablation is performed in the left heart, but this increase is less than when the indication is ventricular tachycardia (2.8%). For the ablation of AF, creation of extensive left atrial lesions has been associated with a high rate of thromboembolic stroke, despite administration of IV heparin and modulated electromagnetic energy. Adjuvant platelet inhibitor therapy to reduce the risk of thromboembolism in this specialized situation is under investigation.

Heparin-Induced Thrombocytopenia (HIT)

HIT is an antibody-mediated adverse reaction to heparin that can result in venous or arterial thrombosis. Diagnosis of HIT is based on both clinical and serological features. Manifestations of the HIT syndrome include an otherwise unexplained fall in platelet count $\geq$50%, even if the nadir remains above 150×10^9/L, or skin lesions at heparin injection sites accompanied by HIT antibody formation. The fall in platelet count almost always occurs between day 5 and day 15 after introduction of heparin but can develop earlier in patients exposed to heparin during the previous 3 months. The frequency of HIT varies in different clinical settings such that the risk of venous thrombosis from HIT is higher in high-risk surgical patients than in medical patients.

The HIT antigen is a multimolecular complex between PF4 and heparin. HIT antibodies bind to regions of the PF4 molecule that have been conformationally modified by its interaction with heparin. The increased propensity to thrombosis in HIT is probably mediated by thrombin generated as a result of in vivo platelet activation, as a consequence of interaction between heparin/PF4/IgG immune complexes with Fc receptors on platelets. A minimum of 12 to 14 saccharides are required to form the antigenic complex with PF4, so heparin molecules with a molecular weight greater than approximately 4,000 Daltons have the potential to cause HIT, and HIT occurs less commonly with LMWH than with UFH.

Diagnosis

Two main classes of laboratory assays have been developed to detect HIT antibodies, activation assays and antigen assays. The use of washed platelets rather than platelet-rich plasma derived from normal donors increases the reliability of activation assays. Of the various activation assays available, those that use washed platelets and platelet serotonin release or heparin-induced platelet activation are most accurate. Antigen assays, now commercially available, that are based on detecting antibodies against PF4 bound to heparin or polyvinylsulfonate respond to clinically insignificant antibodies more often than do activation assays.

Treatment

If HIT is suspected on clinical grounds and the patient either has thrombosis or is at risk of developing thrombosis, heparin should be stopped and replaced with lepirudin (Refludan). Although the diagnosis should be confirmed as soon as practical, treatment should not be delayed. Warfarin should not be used alone, because a recent report suggests this can aggravate the thrombotic process. Lepirudin is a hirudin derivative that does not exhibit cross-reactivity and is manufactured by recombinant technology. Its use in HIT has been approved by the Food and Drug Administration on the basis of 2 prospective cohort studies that compared treatment of HIT-associated thrombosis with lepirudin versus historical controls. An IV infusion is used for rapid therapeutic anticoagulation, beginning with a bolus loading dose of 0.4 mg/kg IV followed by a maintenance dose of 15 mg x kg^{-1} x h^{-1}, with adjustments to maintain aPTT at 1.5 to 2.5 times the median of the normal laboratory range.

In the absence of overt thrombosis, cessation of heparin has long been the cornerstone of management of HIT, but several studies have shown that simply stopping heparin may be inadequate because of the high risk of overt thrombosis in the week after interruption of heparin. Treatment with hirudin should therefore be considered in all patients with HIT who remain at risk of thrombosis, including postoperative patients and those with sepsis. Recombinant hirudin (lepirudin) should be used until the platelet count has recovered (See table 9 of the original guideline document). This should also be considered for patients with acute HIT without thrombosis (isolated HIT), because there is a high risk for subsequent clinically evident thrombosis in these patients. Warfarin should not be used alone to treat acute HIT complicated by DVT because of the risk of venous limb gangrene. When given to patients adequately anticoagulated with lepirudin, warfarin appears safe in acute HIT, but it is prudent to delay starting warfarin until the platelet count has risen above 10 x 10^9/L.

Low-Molecular-Weight Heparins

Anticoagulant Effects

LMWHs have been evaluated in a large number of randomized clinical trials and have been found to be safe and effective for prevention and treatment of venous thrombosis. More recently, LMWH preparations have also been evaluated in patients with acute PE and those with unstable angina.

Prevention of Venous Thrombosis

LMWHs were first evaluated for the prevention of venous thrombosis in high-risk surgical patients in the mid-1980s, and there is now extensive experience with their use for this indication. In patients undergoing general surgery and in high-risk medical patients, low doses of LMWH administered SC once daily are at least as effective and safe as low-dose UFH administered SC 2 or 3 times daily. LMWH has become the anticoagulant of choice for the prevention of venous thrombosis during major orthopedic surgery and in anticoagulant-eligible patients after major trauma. The risk of bleeding with LMWH is small and comparable to that with low-dose heparin.

General Surgery

LMWHs were effective and safe in 2 well-designed randomized trials. One trial in 4,498 patients showed a statistically significant reduction in thromboembolic mortality in favor of LMWH (0.07%) compared with a UFH control group (0.36%). A meta-analysis of randomized trials comparing low-dose heparin with LMWH concluded that there were minimal differences between the 2 forms of prophylaxis.

Summary of LMWH in Orthopedic Surgery and Trauma

Overall, LMWHs appear effective for prevention of venous thromboembolism, and they appear safe for use in high-risk patients undergoing major orthopedic surgical procedures. Compared with placebo, the relative risk reduction for all thrombi and for proximal vein thrombi is approximately 70%. LMWHs are more effective than low-dose heparin, at least as effective as warfarin, and more effective than dextran or aspirin in patients undergoing total hip arthroplasty, and they are more effective than warfarin, aspirin, or dextran in patients undergoing major knee surgery. Similarly, LMWHs are more effective than aspirin in patients with hip fracture. The risk of bleeding with LMWH is comparable to that with low-dose heparin or warfarin. Refer to the original guideline document for more information regarding the use of LMWHs during orthopedic surgery, hip fracture, and multiple trauma.

Neurosurgery

In a recent study comparing LMWH plus compression stockings with compression stockings alone, those assigned to the LMWH group has a risk reduction of 48%. There was no difference in major bleeding.

Medical Patients

LMWHs have been compared with placebo in 2 studies of patients with ischemic stroke and have been compared with low-dose heparin in 2 studies. Compared with placebo, LMWHs reduce the risk of venous thrombosis between 40 and 86% without an increase in clinically important bleeding. In studies comparing LMWHs with heparin, patients randomized to receive LMWH showed a statistically significant >70% relative risk reduction in thrombosis.

Treatment of Venous Thromboembolism

A number of LMWH preparations have been compared with heparin in patients with venous thrombosis and/or PE in well-designed studies. The results of studies published before 1995 that used 4 different preparations have been summarized in a meta-analysis in which the data for each of the 4 LMWHs were pooled separately (See tables 15 and 16 of the original guideline document). All 4 LMWH preparations were as effective and safe as IV heparin, and the rates of recurrent thromboembolism and major bleeding were similar with all of the LMWHs. It is noteworthy that the LMWHs were administered by SC injection in unmonitored, weight-adjusted doses, whereas heparin was monitored by the aPTT.

Since publication of the pooled analysis in 1995, 5 additional large randomized trials have been completed, 2 in patients with venous thrombosis, 1 in patients with venous thrombosis or PE, 1 in patients with PE, and 1 in patients with proximal vein thrombosis who were also randomized to inferior vena cava filter insertion. The design of 2 of the studies capitalized on the more predictable anticoagulant response to LMWH by encouraging patients assigned to LMWH treatment at home, whereas those assigned to heparin were treated conventionally in the hospital with a continuous IV infusion. The results, shown in Table 17 of the original document, indicate that out-of-hospital administration of LMWH to eligible patients with DVT is as effective and safe as IV heparin administered in the hospital. Both studies excluded patients with symptomatic PE or a history of recent previous venous thrombosis. To address this study deficiency, the investigators collaborated in the COLUMBUS study, in which 1,021 patients with venous thrombosis or PE were randomly assigned to treatment with either SC LMWH (riviparin sodium) or adjusted-dose IV UFH for 8 days. Warfarin was started concomitantly and continued for 3 months. The mean hospital stay was 3 days shorter in patients assigned to LMWH, whereas the incidence of recurrent thromboembolism, bleeding, and mortality was similar in both groups.

The relative efficacy and safety of LMWH and heparin for treatment of patients with acute PE have also been investigated in a larger population. Patients who did not require thrombolytic therapy or pulmonary embolectomy (n=612) were randomly assigned to receive LMWH (tinzaparin, 175 anti-factor Xa U/kg SC once daily) or heparin (50 U/kg bolus followed by a continuous infusion of 500 U x kg^{-1} x d^{-1} adjusted to an aPTT ratio of 2.0 to 3.0). The outcome measure, a composite of recurrent thromboembolism, major bleeding, and death, was assessed on days 8 and 90. By day 8, 9 (2.9%) of 308 patients assigned to UFH and 9 (3.0%) of 304 patients assigned to LMWH developed at least 1 of the primary events; by day 90, 22 patients (7.1%) assigned to UFH and 18 (5.9%) assigned to LMWH developed events (P=0.54). The rate of major bleeding was similar in both groups (2.6% and 2.0%, respectively; P=NS). There were 3 deaths at 8 days and 14 deaths (4.5%) at 90 days in those assigned to UFH, and there were 4 deaths at 8 days and 12 (3.9%) at 90 days in patients assigned to LMWH. Five of the deaths in the heparin group were treatment related (3 from PE and 2 from major bleeding) compared with 4 in the LMWH group (3 from PE and 1 from bleeding). The findings of this study combined with those of the COLUMBUS study indicate that SC weight-adjusted LMWH is as effective and safe as IV heparin.

A meta-analysis of 11 randomized studies comparing IV heparin and SC LMWH in approximately 3,500 patients with acute DVT (See table 19 of the original guideline document) found major bleeding to be less frequent in patients treated with LMWH (OR 0.57; P=0.05). The frequency of recurrent thromboembolic events did not differ significantly between treatment groups (OR 0.85; P=0.28), but the mortality rate was lower in those assigned LMWH (OR 0.71; P=0.02). Most of the deaths were not ascribed to PE, so the mechanism for this mortality reduction is uncertain.

Most studies evaluating LMWH preparations for treatment of venous thromboembolism evaluated a twice-daily, weight-adjusted regimen. However, 2 studies using tinzaparin, 1 in patients with acute venous thrombosis and the other in patients with acute PE, used once-daily dosing (175 anti-factor Xa U/kg). Results of comparisons of the efficacy and safety of LMWH administered once or

twice daily found once-daily administration of 2 different LMWH preparations as effective and safe as twice-daily dosing.

Unstable Angina and Non-Q-Wave MI

Although the combination of heparin and aspirin is effective for short-term treatment of patients with unstable angina, between 6% and 15% progress to MI or death within 1 month despite continuing aspirin therapy. The recent success of LMWH for the treatment of venous thromboembolism and the feasibility and safety of out-of-hospital use have led to the evaluation of LMWH preparations administered SC without laboratory monitoring in the setting of unstable angina and non–Q-wave MI. To date, 7 randomized trials evaluating LMWH in patients with unstable angina and non–Q-wave MI have been reported (See table 20 of the original guideline document). Short- and long-term relative risk reductions compared with UFH are shown in Figures 8 and 9 of the original guideline document. The first small trial (n=219) compared nadroparin plus aspirin versus UFH plus aspirin versus aspirin alone using an open-label design. The rate of acute MI, recurrent angina, and urgent coronary revascularization was significantly lower with the LMWH and aspirin combination than with UFH and aspirin or aspirin alone. Subsequent to this, a large, double-blind, placebo-controlled trial in 1,506 patients with unstable angina or non–Q-wave MI (FRISC; FRagmin during InStability in Coronary artery disease) compared 120 U/kg of dalteparin twice daily for 6 days followed by 7,500 anti-factor Xa U once daily for 35 to 45 days with placebo; all patients received aspirin. Compared with placebo, LMWH reduced the risk of death or MI by approximately 80% at 6 days. In addition, the composite end point of death, MI, and need for revascularization was significantly lower in patients treated with LMWH (10.3% versus 5.4%). However, no additional benefit was observed with long-term lower-dose LMWH (7,500 anti-factor Xa U of dalteparin once daily) compared with placebo. After 4 to 5 months of follow-up, the rates of death and MI in the placebo and dalteparin groups was 15.3% and 14.0%, respectively (P=0.41), and the rates of death, MI, or revascularization were 43.6% and 42.7%, respectively (P=0.18). This study established the short-term value of LMWH (dalteparin) for treatment of unstable angina and non–Q-wave MI and added to the data in support of a beneficial effect of heparin and aspirin over aspirin alone in this patient population. However, no effect of moderate-dose LMWH was observed over the long term.

In a third study (FRIC; FRagmin In unstable Coronary artery disease), which used an open, randomized design, dalteparin (120 anti-factor Xa U/kg twice daily) was compared with heparin (5,000-U bolus followed by 1,000-U/h continuous infusion for 6 days) in 1,492 patients with unstable angina or non–Q-wave infarction. This was followed in a second phase by a double-blind study comparing LMWH at a dose of 7,500 U/d with placebo. All patients received aspirin. Both treatment regimens were equivalent in terms of efficacy and safety. At 6 days, the composite outcome of death, MI, or recurrent angina occurred in 7.6% of the heparin group and 9.3% of the LMWH group, whereas the corresponding rates of the composite of death or MI were 3.6% and 3.9%, respectively. Between days 6 and 45, the rate of death, MI, or recurrent angina was 12.3% in both groups. There was no difference in major bleeding, which was infrequent.

The ESSENCE trial (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events) is 1 of 2 studies that compared enoxaparin with heparin.

Patients (n=3,171) with unstable angina or non–Q-wave MI were randomized in a double-blind fashion to 1 mg/kg SC (100 anti-factor Xa U) of enoxaparin every 12 hours or UFH, administered as an IV bolus followed by a continuous infusion, for 2 to 8 days; the median duration of treatment in both groups was 2.6 days (See table 20 of the original guideline document). There was a significant 17% risk reduction in the primary end point of death, MI, or recurrent angina at 14 days with LMWH (P=0.019) and a 15% risk reduction at 30 days (P=0.016). This difference was accounted for mainly by a lower incidence of recurrent angina in patients assigned to LMWH. There was no difference in the incidence of major bleeding at 30 days (6.5% with LMWH versus 7.0% with heparin), but total bleeding was more frequent with the LMWH group (18.4% versus 14.2%), primarily because of bruising at injection sites. At 1 year, the difference in the composite end point remained significant (P=0.022).

TIMI-11B (Thrombolysis In Myocardial Infarction 11B) was a double-blind study comparing enoxaparin (bolus followed by SC injections every 12 hours for 3 to 8 days) and IV heparin (administered for at least 3 days) in 3,910 patients with unstable angina or non-Q-wave MI. The primary outcome was death, MI, or urgent revascularization at 43 days. Patients assigned to LMWH continued SC treatment at a lower dose until day 43, whereas patients assigned initially to heparin received placebo. There was an 18% relative risk reduction in events at 14 days (P=0.029) and a 12% risk reduction at 43 days (P=0.048). The absolute risk reductions were 2.4% and 2.3% at 14 and 43 days, respectively. The difference in treatment duration between UFH (3 days) and enoxaparin (43 days) and the validity of comparing event rates at 14 days render these data questionable. In addition, the lack of effectiveness of enoxaparin beyond 14 days is surprising and fails to establish a role for long-term use of LMWH in this patient population.

Nadroparin was also evaluated in the FRAXIS (FRAXiparine in Ischaemic Syndrome) trial. Patients with unstable angina or non-Q-wave infarction were randomly assigned to receive full-dose SC nadroparin (every 12 hours on days 1 through 6, then placebo from day 7 to day 14), sustained SC nadroparin (every 12 hours for 14 days), or initial IV heparin (on days 1 through 6, followed by placebo until day 14). The incidence of the primary outcome (cardiovascular death, MI, and refractory or recurrent angina) was no different among the 3 groups at 6 days, and there was no difference between short- and long-term treatment with LMWH by 14 days.

Another recent trial evaluated long-term administration of LMWH compared with placebo. FRISC-II (Fragmin and Fast Revascularisation during InStability in Coronary artery disease) was a randomized, placebo-controlled trial of dalteparin in 2,267 patients with unstable angina and non-Q-wave-MI. All patients received dalteparin 120 IU/kg every 12 hours for the acute phase (5 to 7 days) and then were randomized to dalteparin 5000 to 7500 IU every 12 hours or placebo for 90 days. The primary outcome was the composite of death and MI at 3 months. The primary outcome rates did not differ significantly between the dalteparin and placebo groups (6.7% versus 8.0%, P=0.17), but the rates of major and minor bleeding were significantly higher in patients who received dalteparin (3.3% versus 1.5%, P<0.01 and 23.0% versus 8.4%, P<0.001), respectively. A meta-analysis of the 2 trials of enoxaparin (ESSENCE268 and TIMI-11B270) showed

that compared with UFH, enoxaparin produced a 20% relative reduction in rates of death and MI during the first 7 to 14 days of treatment.

The reason for the observed differences across trials that evaluated short-term LMWH compared with UFH in the presence of aspirin (the FRIC and FRAXIS versus ESSENCE and TIMI-11B studies) is not clear. Potential explanations include true therapeutic differences between the LMWH agents and differences in trial design, administration of UFH, and patient population, or the play of chance. To determine definitively whether enoxaparin is superior to other LMWH preparations would require head-to-head comparisons within 1 or more trials.

When all trials that compared short-term LMWH with UFH were pooled (n=12,171), an OR of 0.85 (95% CI 0.70 to 1.04) was derived, which suggests a modest 15% reduction with LMWH over UFH (See figure 8 of the original guideline document). Data from approximately 10,000 patients in long-term trials do not indicate a benefit of LMWH over placebo in reducing MI or death (OR 1.04; 95% CI 0.79 to 1.37; see figure 9 of the original guideline document). It is of interest to consider these results with LMWH in unstable angina and non–Q-wave MI in light of experience with platelet GP IIb/IIIa antagonists and direct thrombin inhibitors. Because LMWH has not been compared directly with either of these classes of antithrombotics agents, however, only indirect inferences are possible, and these may be misleading.

Heparin has been compared with the synthetic GP IIb/IIIa blocker, lamifiban, in the PARAGON trial (Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network) and with tirofiban in the PRISM trial (Platelet Receptor Inhibition in Ischemic Syndrome Management). When used alone, neither GP IIb/IIIa antagonist was more effective than heparin. The PURSUIT trial (Platelet Glycoprotein IIb/IIIa in Unstable Angina Receptor Suppression Using Integrilin Therapy) evaluated 9450 patients and showed that a 72-hour infusion of Integrilin was associated with a 15 to 20% relative reduction in death and MI. Both the CAPTURE trial (C7E3 fab AntiPlatelet Therapy in Unstable Refractory angina), which evaluated abciximab in 1,265 patients, and the PRISM-PLUS trial, which evaluated tirofiban in 1915 patients, focused on high-risk patients with unstable coronary artery disease. In both studies, GP IIb/IIIa inhibitors produced a 30% to 50% relative reduction in death or MI with treatment before and during revascularization.

Hirudin, a bivalent direct thrombin inhibitor, was evaluated in the OASIS-2 (Organization to Assess Strategies for Ischemic Syndromes) trial, a randomized study of 10,141 patients with unstable coronary artery disease assigned to either 72 hours of IV hirudin or standard heparin. There was a 10 to 20% relative reduction in the incidence of death or MI with hirudin in the first 3 to 7 days, but this was associated with an increase in bleeding (major bleeding in 1.2% versus 0.7% of patients and minor bleeding in 7.6% versus 4.5% of patients with hirudin and heparin, respectively).

Thus, 3 new classes of antithrombotic agents—LMWH (such as enoxaparin), platelet GP IIb/IIIa antagonists (such as abciximab), and thrombin inhibitors (such as hirudin)—are available for treatment of patients with unstable angina and non-Q-wave infarction. It appears that it is necessary to combine GP IIb/IIIa antagonists with heparin to achieve optimal efficacy. Because the efficacy of these

new anti-thrombotic agents is limited to the initial period of acute treatment, the challenge is to develop safe and effective regimens that require simple or no monitoring and that are convenient for outpatient use to reduce the 15% risk of new MI over 3 months.

Q-Wave MI

Experience with LMWH in patients with acute Q-wave MI is limited to 2 small studies in which the majority of patients received thrombolytic therapy. The Fragmin in Acute Myocardial Infarction (FRAMI) study enrolled 776 patients with acute anterior MI in a randomized, double-blind comparison of LMWH (dalteparin at 150 U/kg SC twice daily during hospitalization) with placebo. Thrombolytic therapy (streptokinase) and aspirin were administered to 91.5% and 97.6% of patients, respectively. The mean time to the start of treatment was approximately 12 hours in both the dalteparin and placebo groups. The primary end point was the composite of left ventricular mural thrombus formation diagnosed by echocardiography and systemic arterial embolism by day 92. Of the 517 patients with echocardiograms available for analysis, thrombus formation, embolism, or both developed in 59 (21.9%) of 270 patients in the placebo group and 35 (14.2%) of 247 patients receiving dalteparin (P=0.03). Benefit was predominantly a consequence of decreased left ventricular thrombus formation. The relative risk of thrombus formation with LMWH treatment was 0.63 (95% CI 0.43 to 0.92, P=0.02). Analyses of all randomized patients revealed no significant difference between treatments with respect to arterial embolism (6 versus 5 patients, respectively), reinfarction (8 versus 6 patients), or death (23 patients in each group). LMWH therapy was associated with an increased risk of both major (2.9% versus 0.3%, P=0.006) and minor (14.8% versus 1.8%, P<0.001) hemorrhage. One nonfatal and 2 fatal cerebral hemorrhages (verified by CT scan) occurred in the LMWH group. Thus, although LMWH reduced left ventricular thrombus formation in patients with acute anterior MI, its use was associated with a significantly increased risk of major hemorrhage, possibly a consequence of concomitant thrombolytic therapy and a higher dose of dalteparin than used in either the FRISC or FRIC studies.

In a small study of 103 streptokinase-treated patients randomly assigned to enoxaparin (40 mg/d for 25 days) or placebo within 5 days of acute MI, 2 (4.3%) of 43 patients in the enoxaparin group developed recurrent MI within 30 days compared with 12 (20%) of 60 patients receiving placebo (P=0.02). The BIOMACS II study (Biochemical Markers in Acute Coronary Syndromes), a phase III clinical trial, is currently in progress in Scandinavia to address this issue.

Coronary Angioplasty

Studies in laboratory animals indicating that LMWH suppresses neointimal proliferation after arterial balloon injury prompted clinical trials to evaluate the effect of LMWH on the rate of restenosis after angioplasty. In the Enoxaparin Restenosis after Angioplasty (ERA) trial, 282 patients were randomly assigned to receive either 40 mg of enoxaparin or placebo SC once daily for 1 month after successful coronary angioplasty. Angiographic or clinical restenosis occurred in 51% of the 231 patients receiving placebo and 52% of the 227 patients receiving enoxaparin (P=0.625). Although major bleeding was more common in the enoxaparin group, the rate of major bleeding did not differ significantly. The

Enoxaparin and MaxEPA for the Prevention of Angioplasty Restenosis (EMPAR) study randomly allocated 653 patients to either enoxaparin (30 mg SC twice daily) or placebo for 6 weeks after successful angioplasty, with randomization to either fish oil or control a median of 6 days earlier. Quantitative coronary angiography revealed no significant difference in the rate of restenosis either per patient or per lesion. The results of these 2 negative studies leave little doubt as to the lack of efficacy of enoxaparin in preventing restenosis when used in doses of up to 60 mg/d (6000 anti-factor Xa U/d) for 6 weeks.

Atrial Fibrillation

The multicenter, randomized, double-blind Heparin in Acute Embolic Stroke Trial (HAEST) found no evidence that LMWH is superior to aspirin for treatment of acute ischemic stroke in patients with AF. In that study, either the LMWH, dalteparin (100 U/kg SC twice daily), or aspirin (160 mg/d) was started within 30 hours of stroke onset in 449 patients with AF and acute ischemic stroke. The frequency of recurrent ischemic stroke during the first 14 days was 8.5% in dalteparin-allocated patients versus 7.5% in aspirin-allocated patients (OR 1.13, 95% CI 0.57 to 2.24). There was no benefit of dalteparin compared with aspirin in reducing cerebral hemorrhage (12% versus 14%), progression of symptoms within the first 48 hours (11% versus 8%), or death (9% versus 7%, all P=NS) or functional outcome at 14 days or 3 months.

LMWH has also been used in patients with AF as an adjunct to the strategy of transesophageal echocardiography-guided cardioversion but has not been specifically evaluated in a controlled trial. In one observational series, 242 patients referred for cardioversion of AF or flutter without prior anticoagulation were examined by transesophageal echocardiography. Those subjected to prompt cardioversion (n=162; mean age 62 years) were younger than others treated conventionally with warfarin before cardioversion (n=80; mean age 67 years; P<0.05) and more often had "lone" AF or flutter without associated heart disease (53% versus 34%, P<0.05). Dalteparin was administered together with warfarin before early cardioversion of these low-risk patients and continued until the international normalized ratio reached the therapeutic range. Although no ischemic events were observed, more systematic experience must be gained in AF patients across a broader range of intrinsic thromboembolic risk before LMWH can be routinely advocated before cardioversion.

Conclusions

LMWH preparations are at least as effective and safe as UFH and more convenient, although they have the disadvantage of expense. The higher cost of the drug itself cannot be considered in isolation, however, because savings from SC administration and reduced hospital stay offset this. One appealing feature of LMWH is a more predictable dose response relative to UFH, which translates clinically into weight-adjusted dosing without laboratory monitoring. The only study that compared the predictability of the dose response of LMWH with that of UFH demonstrated less variability, but this was not abolished entirely. The efficacy and safety of LMWH might be improved by monitoring anti-factor Xa levels, but the anticipated improvement in clinical outcome would likely be marginal and balanced by inconvenience and added expense. Weight-adjusted dosing could be misleading in patients with renal insufficiency and in obese patients. Further

studies are required to determine whether monitoring is necessary in such patients. Based on current information, however, LMWH preparations should be administered with weight-adjusted dosing in the majority of patients.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting each recommendation is not specifically stated. Whenever possible, the recommendations in this review of anticoagulant therapy are based on results of well-designed clinical trials. For some indications or clinical subgroups, however, recommendations are of necessity based on less solid evidence and are therefore subject to revision as new information emerges from future studies.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Increased knowledge and awareness by healthcare professionals of effective, state-of-the art science related to the use of anticoagulant therapy

POTENTIAL HARMS

Risks associated with anticoagulant therapy, including bleeding and heparin-induced thrombocytopenia, are discussed in the "Major Recommendations" section of this summary.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Heart Association Web site:

- HTML Format
- Portable Document Format (PDF)

Print copies: Available from the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596; Phone: 800-242-8721.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on September 13, 2004. The information was verified by the guideline developer on October 13, 2004.

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